PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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Applicant's or agent's file reference 871	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/PL2005/000024	International filing date *(day/month/year)* 02.04.2005	Priority date *(day/month/year)* 02.04.2004
International Patent Classification (IPC) or national classification and IPC INV. C07D401/04 A61K31/506 A61P35/00 C07D401/00		
Applicant INSTYTUT FARMACEUTYCZNY et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 8 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30.01.2006	03.05.2006
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Schmid, A Telephone No. +49 89 2399-8591

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/PL2005/000024

Box No. I Basis of the report

1. With regard to the **language**, this report is based on

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3(a) and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4(a))
   - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

2-48	as originally filed
1	received on 30.01.2006 with letter of 26.01.2006

Claims, Numbers

1-22	received on 30.01.2006 with letter of 26.01.2006

Drawings, Sheets

1/12-12/12	as originally filed

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☒ the claims, Nos. 8,8a
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has, within the applicable time limit:

   ☒ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest and, where applicable, the protest fee.

   ☐ paid additional fees under protest but the applicable protest fee was not paid.

   ☐ neither restricted the claims nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is:

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-7,8,8a,10-22
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-7,8,8a,10-22
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-7.8.8a,10-22
	No:	Claims	

2. Citations and explanations (Rule 70.7):

   see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item IV
Lack of unity of invention

1) The examiner agrees to the findings of lack of unity and the arguments supporting these objections as could be found in the search report.

Invention 1:

Re Item V
Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The present claim 1 clearly differs from the closest prior art formed by WO-A-99 03854 (D1) in the stoichoimetric ratio of the reactants.

Accordingly the present subject-matter is novel pursuant to Article 33(2) PCT.

2) WO-A-99 03854 which forms the closest prior art does not allow to selectively prepare the α-crystal form of imatinib methanesulfonate. Accordingly, there was a need for a process in order to solve this problem. Unexpectedly, the above difference to the prior art allows to obtain a pure α-crystal form of imatinib monomesylate which was not possible in D1 (cf. above). Moreover, it appears that this feature allows to extend the range of usable solvents whereas D1 was limited to certain ones (cf D1, page 7, 2nd paragraph).

Accordingly, the subject-matter of present claims 1-7 and 10-13 (as far as they depend on claims 1-7) is also inventive pursuant to Article 33(3) PCT.

3) Present claim 8 is now independent from the claim 1.

Present claim 8 has been based on the priority application P-366885 (cf. original page 4). However, the discussed method only forms a "prior art" which has been improved by the specific ratio (cf. original page 11, lines 16, 17) as mentioned below and does **not** form a part of the invention.

Accordingly, it cannot serve as a basis for an amended claim. The same applies for present claims 8a which contains more specific information.

Accordingly, present claims 8 and 8a go beyond the original description.

Being dependent from claim 1, present claims 8 and 8a meet the requirements of Article 33(2) PCT and Article 33(3) PCT.

Re Item VIII

Certain observations on the international application

1) The applicant has filed new claims including a claim "8a" followed by a claim 10, but omitting a claim 9 which has to be considered to be unclear in sense within the meaning of Article 6 PCT.

Accordingly, the set of claims has to be renumbered when entering the regional phase.

Invention 2:

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1) The subject-matter differs from the prior art represented by WO-A-2004/026930 (D2) as example for the mesylate salt of imatinib in the fact that it concerns **di**methanesulfonic salt of imatinib instead of the known monomethanesulfonic salts.

Accordingly the subject-matter of present claims 14-22 is novel pursuant to Article 33(2) PCT.

2) However, looking at D2, page 5, paragraph [0023] it becomes clear that a lot of pharmaceutically acceptable addition salts are possible within the general knowledge of a skilled person including methane sulfonic acid salts.

Accordingly, it would be obvious for a skilled person looking for alternative salts of mesylates of imatinib to synthesize the **di**mesylate salt thereof which has been done by the applicant. However, looking at the present description only physico-chemical properties of these compounds are described. No proof exists whether the dimesylates show any effect, irrespective the fact that superior effects had to be demonstrated in order to acknowledge an inventive step.

Therefore, no inventive step with respect to Article 33(3) PCT can be acknowledged to the subject-matter of present claims 14-22.

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Polymorphs of acid addition salts of Imatinib with methanesulfonic acid

Field of the invention

The invention relates to the polymorphs of acid addition salts of Imatinib with methanesulfonic acid and to the processes for their preparation. In particular, the invention relates to the process for the preparation of Imatinib methanesulfonate α-crystal form.

The related art

Imatinib, 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-yloamino]phenyl]benzamide, has been disclosed in the European Patent Application EP 0564409 A1 as a pharmacologically active substance of anti-tumour activity, especially useful in the treatment of diseases which respond to an inhibition of the receptor tyrosine kinase.

The International Patent Application WO 2004/026930 relates to the use of imatinib or a pharmaceutically acceptable salt thereof for reducing inflammation. Many pharmaceutically acceptable addition salts of imatinib are mentioned, although the experimental studies with monomethanesulfonate salt only are described in details.

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What we claim is:

1. A process for the preparation of the α-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide comprising:

a) carrying out the addition reaction using not more than 0.99 equivalents of methanesulfonic acid per 1 equivalent of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide, in a solvent selected from the group consisting of C_2-C_6 aliphatic alcohols or the mixtures thereof, optionally with the addition of the other C_1-C_4 aliphatic alcohol;

b) adding, if necessary, a solvent selected from the group consisting of the esters of lower carboxylic acids and C_1-C_4 aliphatic alcohols;

c) optionally inoculating the reaction mixture with the α-crystal form;

d) stirring the reaction mixture for the time necessary for crystallization of the α-crystal form;

e) isolating the α-crystal form from the reaction mixture.

2. The process according to claim 1 in which the addition reaction is carried out using from 0.95 to 0.99 equivalents of methanesulfonic acid per 1 equivalent of

4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl] benzamide.

3. The process according to Claims 1-2, in which the addition reaction is carried out in an alcohol selected from the group comprising *n*-propyl alcohol, isopropyl alcohol, *n*-butyl alcohol, *tert*-butyl alcohol and the mixtures thereof with ethyl alcohol.

4. The process according to Claims 1-3 in which the addition reaction is carried out in the mixture containing from 0 to 50% of ethyl alcohol and from 50 to 100% of n-propyl alcohol (v/v).

5. The process according to Claims 1-3 in which the addition reaction is carried out in the mixture containing from 0 to 50% of ethyl alcohol and from 50 to 100% of isopropyl alcohol (v/v).

6. The process according to Claims 1-3 in which the addition reaction is carried out in the mixture containing from 0 to 50% of ethyl alcohol and from 50 to 100% of n-butyl alcohol.

7. The process according to Claims 1-3 in which the addition reaction is carried out in the mixture containing from 0 to 50% of ethyl alcohol and from 50 to 100% of *tert*-butyl alcohol.

8. A process for the preparation of the α-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[4-pyridin-3-yl)pyrimidin-2-ylamino]phenyl]benzamide comprising:

a) carrying out the addition reaction using 1 equivalent of methanesulfonic acid per 1 equivalent of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in the ethyl alcohol, optionally with the addition of the other C_1-C_4 aliphatic alcohol;

b) adding a solvent selected from the group consisting of the esters of lower carboxylic acids and C_1-C_4 aliphatic alcohols;

c) inoculating the reaction mixture with the α-crystal form;

d) stirring the reaction mixture for the time necessary for crystallization of the α-crystal form;

e) isolating the α-crystal form from the reaction mixture.

8a. The process according to claim 8 in which the additional C_1-C_4 aliphatic alcohol is methyl alcohol or isopropyl alcohol and wherein the proportion of C_1-C_4 aliphatic alcohol in a solvents mixture do not exceed 55% (v/v).

10. The process according to Claims 1-8a in which the addition reaction is carried out with stirring while maintaining internal temperature of the mixture within the range from room temperature to boiling temperature of the reaction mixture.

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11. The process according to Claims 1-8a in which the α-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide thus obtained is essentially free of the β-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide or any other crystalline solids.

12. The process according to Claims 1-11 in which the α-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide thus obtained shows on X-ray powder diffraction diagram peaks at 2θ angles of approximately: 4.9; 18.6; 19.1; 23.2 and 28.6°, obtained for radiation of CuKα and the wavelength λ=1,54056 Å.

13. The process according to Claims 1-12 in which the α-crystal form of the methanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide thus obtained shows on X-ray powder diffraction diagram the peaks of relative intensity over 20% at 2θ angles of approx.: 10.5; 14.9; 16.5; 17.7; 18.1; 18.6; 19.1; 21.3; 21.6; 22.7; 23.2; 23.8; 24.9; 27.4; 28.0 and 28.6°.

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14. Dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide.

15. Dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in a crystalline form.

16. Dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in a crystalline Form I which shows on X-ray powder diffraction diagram obtained for radiation of CuKα at the wavelength λ=1.54056 Å peaks of relative intensity over 20% at 2θ angles about: 16.94, 19.80, 20.08, 20.51, 21.28, 21.65, 21.98, 22.70 and 23.07°.

16. Dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in a crystalline Form I according to Claim 15, characteristic in that its X-ray powder diffraction diagram obtained for radiation of CuKα at the wavelength λ=1.54056 Å is essentially identical with that presented on Fig. 8.

17. Dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in a crystalline Form II which shows on X-ray powder diffraction diagram obtained for radiation of CuKα at the wavelength

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λ=1.54056 Å peaks of relative intensity over 20% at 2θ angles about: 17.23, 17.62, 18.72, 19.90, 20.23, 21.25, 21.59, 22.05, 22.44, 23.38, 23.68, 24.48, 25.41, 26.10 and 28.39°.

18. Dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide in a crystalline Form II according to Claim 17, characteristic in that its X-ray powder diffraction diagram obtained for radiation of CuKα at the wavelength λ=1.54056 Å is essentially identical with that presented on Fig. 9.

19. A mixture of the crystalline Forms I and II of dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide which shows on X-ray powder diffraction diagram obtained for radiation of CuKα at the wavelength λ=1.54056 Å peaks of relative intensity over 20% at 2θ angles about: 16.91, 17.60, 18.69, 19.78, 20.50, 21.60, 22.00, 22.70, 23.07, 24.49, 26.13 and 27.25°.

20. The mixture of the crystal Forms I and II of Dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide according to Claim 19, characteristic in that its X-ray powder diffraction diagram obtained for radiation of CuKα at

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the wavelength λ=1.54056 Å is essentially identical with that presented on Fig. 10.

21. The use of any of the crystalline form of dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide selected from the group comprising the Forms I and II and the mixtures thereof, for the preparation of a pharmaceutical composition having anti-neoplastic activity.

22. The pharmaceutical composition of dimethanesulfonic acid addition salt of 4-(4-methylpiperazin-1-ylmethyl)-N-[4-methyl-3-[(4-pyridin-3-yl)pyrimidin-2-ylamino)phenyl]benzamide selected from the group comprising the crystalline forms I and II and the mixtures thereof, together with the pharmaceutically acceptable carriers and/or excipients.

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